The Glass Transition Temperature of the β-Relaxation as the Major Predictive Parameter for Recrystallization of Neat Amorphous Drugs

Eric Ofosu Kissi[†], Holger Grohganz[†], Korbinian Löbmann[†], Michael Ruggiero[‡], J. Axel Zeitler[‡], Thomas Rades*[†]

[†]Department of Pharmacy, University of Copenhagen, Universitetsparken 2, 2100 Copenhagen, Denmark
[‡]Department of Chemical Engineering and Biotechnology, Philippa Fawcett Drive, Cambridge, CB3 0AS, United Kingdom.

ABSTRACT

Recrystallization of amorphous drugs is currently limiting the simple approach to improve solubility and bioavailability of poorly water-soluble drugs by amorphization of a crystalline form of the drug. In view of this, molecular mobility, α-relaxation and β-relaxation processes with the associated transition temperatures $T_{g\alpha}$ and $T_{g\beta}$, was investigated using dynamic mechanical analysis (DMA). The correlation between the transition temperatures and the onset of recrystallization for nine amorphous drugs, stored at dry conditions at a temperature of 296 K, was determined. From the results obtained, $T_{g\alpha}$ does not correlate with the onset of recrystallization at the experimental storage conditions. However, a clear correlation between $T_{g\beta}$ and the onset of recrystallization was observed. It is shown that at storage temperature below $T_{g\beta}$, amorphous nifedipine retains its amorphous form. Based on the correlation, an empirical correlation is proposed for predicting the onset of recrystallization for drugs stored at 0% RH and 296 K.

Keywords: Amorphous materials, crystal growth, α-relaxation and β-relaxation, dynamic mechanical analysis (DMA), physical stability, glass transition

INTRODUCTION

The use of amorphous, rather than crystalline, form of drugs in the formulation of active pharmaceutical ingredients to oral dosage forms has gained significant interest due to the apparent increase in solubility of the amorphous form compared to their crystalline counterparts. This is indeed a promising approach to overcome the poor water solubility challenge that an estimated 70% of pharmacologically relevant new chemical compounds suffer from[1], which impedes their development to oral dosage forms. However, since amorphous solids are thermodynamically unstable, they tend to undergo spontaneous crystallization, limiting their overall utility. Despite the significant research interest in this area, there is only a hand-full of often complex methods attempting to predict the onset of recrystallization of amorphous drugs [2-3]. Physical instability (here expressed as the onset of recrystallization), is the rate-limiting step in the development of neat amorphous drugs for routine use in oral dosage forms, such as tablets or capsules. The conversion from the amorphous form to the crystalline form is influenced *inter alia* by the relative humidity the amorphous form is exposed to [4], thermodynamic parameters [5-9], thermal history [10] and the preparation technique used [11]. The molecular processes involved in recrystallization are complex and the thermal and thermodynamic parameters, which have been well studied, do not give sufficient information on this complex process. This leaves molecular mobility as a possibly relevant parameter in the recrystallization process [12-13].

Molecular mobility comprises of intramolecular and intermolecular motions that can be vibrational, translational, and/or rotational [14]. Generally, amorphous compounds exhibit two types of molecular mobility (relaxation), termed global and local mobility. The global mobility is also called primary (α-) relaxation and is responsible for the glass transition temperature, $T_{g\alpha}$, [12, 15]. The physics of the $T_{g\alpha}$ have not been fully explored, however, it is the temperature at which molecular mobility is cooperative in nature leading to a change from a glassy form to the rubbery (super-cooled melt) form [16]. In the amorphous pharmaceutical field, the $T_{g\alpha}$ is mostly studied using differential scanning calorimetry (DSC) [17]. At the $T_{g\alpha}$, which we must emphasize as a temperature range rather than a single temperature, there is a substantial sigmoidal change in the heat capacity of the sample resulting in an increase in the total heat flow.

The local mobility, also called secondary (β-) relaxation, has a lower activation energy compared to the α-relaxation [18] and is therefore observed at temperatures below the $T_{g\alpha}$ [16] and classified as a sub-$T_{g\alpha}$ relaxation. The study of β-relaxation and crystallization processes are of prime importance as it has been shown that there might be a connection between these two processes [19-25]. In this study, dynamic mechanical analysis (DMA) was used to probe temperature dependent mechanical response of nine amorphous drugs, five of which were made amorphous by quench cooling (QC) and four were already amorphous drugs. DMA is a technique used to analyze the mechanical properties of a material as a function of temperature or time, and temperature-dependent discontinuities in these phenomena arising from the amorphous glass transitions are readily apparent with this method. In the isochronal mode (fixed frequency temperature ramping), an oscillatory stress is applied to the sample at a selected frequency and the resulting strain is measured. The difference in the phase angle between stress and strain is measured and mechanical properties such as viscosity (loss modulus E"), elasticity (storage modulus E') and the damping parameter (tan δ) can be determined as a function of

temperature [26-30]. It is important to note that DMA does not probe the fundamental dielectric relaxations (which are measured using electromagnetic radiation), but rather the mechanical response of materials that exhibit the same temperature-dependence as these motions due to a fundamental dependence of both properties on the bulk potential energy landscape.[31]

The objective of this study is to characterize the temperature dependent mobility of a set of amorphous drugs and determine which of the transition temperatures is responsible for the crystallization of the set of amorphous drugs upon storage at 0% RH.

METHODS AND MATERIALS

Materials

Nine drugs were chosen for this study. Indomethacin was obtained from Fagron (Copenhagen, Denmark), nifedipine from Hangzhou Dayangchem Co. Ltd (Hangzhou, China), carvedilol from Cipla Ltd (Mumbai, India), cimetidine from Hawkins (Minneapolis, USA), celecoxib from Dr. Reddy's (Hyderabad, India), the marketed amorphous drug; zafirlukast, from Godenbridge Pharma, Inc (California, USA), Na Taurocholate from Sigma-Aldrich (Steinheim, Germany), Zent X and Zent V from Zentiva k. s. (Prague, Czech Republic).

Preparation of amorphous drugs

The crystalline drugs were melted in aluminum pans at approx.10 K above their melting points on a hot plate. The melts were allowed to cool on a cold surface at RT and milled with mortar and pestle to obtain powders for subsequent analysis. The already amorphous drugs were used as received.

X-ray powder diffraction (XRPD)

XRPD measurements were performed using a PANalytical X-Pert PRO X-ray diffractometer (Almeo, Netherlands). The samples were exposed to Cu K-α radiation (λ=1.54187 Å) using a voltage of 45 kV and current of 40 mA. All measurements were performed in reflection mode from 5 – 30° 2θ using a scanning speed 0.058° 2θ/s and a step size of 0.026° 2θ.

Physical stability studies

Physical stability studies were performed on the quench cooled amorphous drugs. The samples were stored at 0% RH using phosphorous pentoxide (P_2O_5) at 298 K. XRPD measurements for the first sample set were performed on a weekly basis for the first 8 weeks. Samples that did not show signs of crystallization were measured monthly from then on. The second set of samples, amorphous nifedipine stored at 0% RH at different temperatures (273 K, 296 K and 313 K), was measured on day 1, 4, 7 and weekly from then on. For nifedipine stored at 0% RH at 253 K and 193 K, XRPD measurements were made monthly. For the physical stability of the already (practically stable) amorphous drugs used, the onset of recrystallization (1/time) was set to $1e^{-7}$.

Dynamic mechanical analysis (DMA)

Powdered amorphous drugs were evenly loaded onto the lower tray of a stainless-steel powder pocket. With the powder pocket lid in place, the sample was loaded into a 35 mm dual cantilever clamp of a

DMA Q800 (TA Instruments- Waters LLC, New Castle, DE, USA) fitted with a gas cooling accessory connected to a liquid nitrogen dewar. The DMA detects mechanical changes using an optical encoder (approx. 1nm resolution) and are more sensitive towards detection of glass transitions than heat capacity changes as in a DSC.

DMA scans were performed in a multi-frequency-strain mode where the sample is heated linearly whilst deforming the sample in an oscillatory manner. Measurements were performed at a frequency of 1 Hz, amplitude of 20.00 μm and a heating rate of 3 K/min from 153 K up to the DMA measured glass transition temperature, of the sample. Once the β-relaxation region was observed, repeated measurements were made in triplicate starting at approximately 20 K below the onset of β-relaxation. Data analysis was performed using Trios® software.

RESULTS AND DISCUSSION

The data obtained from the DMA measurements of the model drugs, as shown in Figure 1 for amorphous indomethacin, is from the tan δ signal. Upon freezing at 153 K and reheating the amorphous drugs at a heating rate of 3 K/min, a sharp peak is observed and its maximum was taken as $T_{g\alpha}$. In the sub-$T_{g\alpha}$ range a broad peak was also observed which is assigned to the β-relaxation.

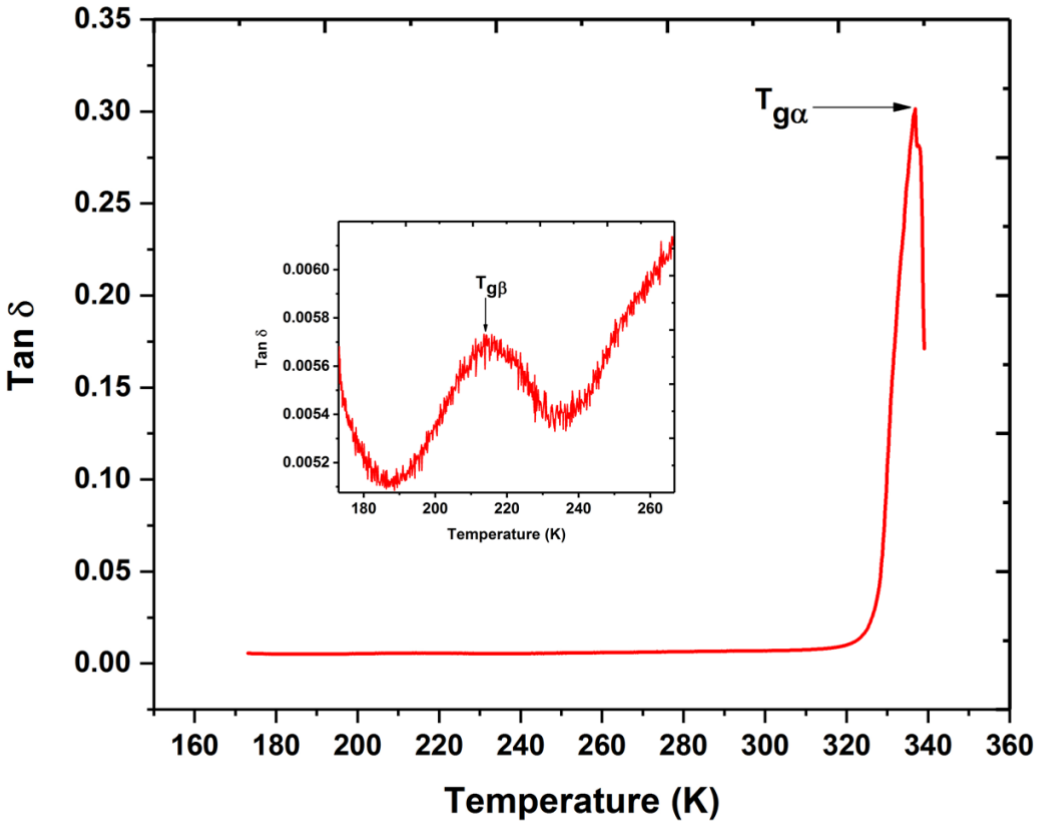


Figure 1: Tan δ response for amorphous indomethacin. The insert is a zoomed-in section from 173 K to 273 K which shows the β-relaxation.

The peak maximum of this broad peak was taken as the secondary glass transition temperature, $T_{g\beta}$ (as shown in Figure 1 on the example of amorphous indomethacin, other examples are in the supporting information). The observed $T_{g\alpha}$ and $T_{g\beta}$ are from isochronal measurements at 1Hz, where the approximate DMA relaxation time is 0.159s. The broad peak was observed for all the amorphous drugs indicating that all the drugs possess local relaxations and hence, are mobile below their $T_{g\alpha}$. It is worth noting that in some polymeric materials, there are multiple secondary relaxations and some are linked to side chain motions [31]. However, in small drug molecules which do not contain such repeating units, as found in polymeric materials, the observed secondary relaxations may be arising from localized molecular motion [32] which has been identified as an intrinsic property of disordered molecular glasses [16]. This type of mobility is termed Johari-Goldstein relaxation [31] and has been found in a terahertz spectroscopic study on amorphous organic molecules [33], in metallic glasses using DMA [34] and in viscous liquids using dielectric spectroscopy [35]. Other techniques that have been used in the study of glass transitions are Brillouin scattering [36], neutron scattering [37], Raman spectroscopy [38] and ^{2}H-NMR spin lattice relaxation [39] among others. However, DSC which is a well-established and comparatively simple technique, most often used in pharmaceutical development, cannot easily

resolve the β-relaxation in amorphous drugs [19], as the change in heat capacity at that temperature may be below the detection limit. This has led to a focus on the $T_{g\alpha}$ especially in the amorphous drug community with only comparatively little work done on the $T_{g\beta}$ [40]. It has been recently shown that a weak but distinct signal change of the β-relaxation process can be detected in the techniques mentioned above [41], and it is perhaps not surprising that this change may be below the detection limit of a DSC. However, Vyazovkin et al. detected $T_{g\beta}$ with DSC after annealing [40] and Oguni detected such transitions using specialized DSC equipment [42], but these have been more commonly interpreted by the wider community as to originate from potential cracks in the sample.

Here, we report for the first time sub-$T_{g\alpha}$ relaxations of amorphous drugs measured via DMA. There is still debate regarding the fundamental physical mechanism governing the mobility below $T_{g\alpha}$. A number of theories using concepts ranging from the so-called 'island of mobility'[16] to 'caged dynamics'[32, 43-45] have been proposed. Recently, an investigation into the origins of the molecular dynamics in disordered solids has suggested that the potential energy surface structure, i.e. energetic peaks and valleys, are directly responsible for the relaxation processes found in molecular glasses. Specifically, the glass transitions represent the points at which there is sufficient energy to overcome the potential barriers, leading to increased motion and thus increased molecular mobility. At temperatures below $T_{g\alpha}$, the mobility is much more localized (i.e. intramolecular torsions and hindered rotations), and below $T_{g\beta}$ it was shown that these types of motion are frozen out. In this study, we show that a correlation exists between this sort of sub-$T_{g\alpha}$ molecular mobility and the onset of recrystallization of amorphous drugs.

In order to investigate the onset of recrystallization, a set of the amorphous drugs was prepared (originally crystalline drugs were converted to their respective amorphous forms by QC) and were stored over phosphorus pentoxide, P_2O_5, (0% RH) at 296 K. The onset of recrystallization was monitored by X-ray powder diffraction (XRPD), in an attempt to establish a correlation between either the $T_{g\alpha}$ or $T_{g\beta}$ and the onset of recrystallization.

The $T_{g\alpha}$, observed by DMA as the peak maximum of the sharp peak in Figure 1, is often assumed to correlate with stability. However, when plotting the $T_{g\alpha}$ versus the onset of recrystallization (1/time) it is obvious (see Figure 2) that there is no clear relation between the $T_{g\alpha}$ and the physical stability of the amorphous drugs at the chosen storage condition. For example, nifedipine and indomethacin have similar molecular weight and $T_{g\alpha}$ but they do show vast difference in their recrystallization tendencies; the onset of recrystallization for nifedipine is 1 day and that of indomethacin is 30 days when stored at 0% RH, 298 K. However, the fact remains that the $T_{g\alpha}$ is important as it is the vitrification temperature. For pharmaceutical development of amorphous drugs, it remains an indispensable parameter as it determines the upper temperature limit for manufacturing and storage.

The importance of $T_{g\beta}$ as determined by DMA for physical stability is shown in Figure 3. Clearly, there is a good correlation between $T_{g\beta}$ and the onset of recrystallization of the amorphous drugs. Drugs with lower $T_{g\beta}$, e.g. nifedipine ($T_{g\beta} \approx 89$ K below storage temperature), tend to recrystallize earlier than those with higher $T_{g\beta}$, e.g. Zent V that has $T_{g\beta} \approx 75$ K above the experimental storage temperature. As shown above, $T_{g\beta}$ represents the lower-limit of the thermal energy required to overcome potential energy barriers related to conformational rearrangement, increasing the molecular

mobility. This increased mobility increases the probability that two neighboring molecules will move into a favorable (crystalline) packing motif, which could set off a chain of crystallization events. Therefore, storing amorphous drugs at temperatures above $T_{g\beta}$ may lead to increased molecular mobility, increased rate of nucleation and subsequently, increased propensity for crystallization. For an amorphous drug to be physically stable it is imperative that $T_{g\beta} \geq T_s$ (storage temperature), as it has been clearly shown by the already amorphous (i.e. practically stable), zafirlukast, Na-taurocholate, Zent X and Zent V, used in this study; all of them have a $T_{g\beta}$ at or above ambient temperature. If the $T_{g\beta}$ of the neat amorphous drug is at room temperature or higher, molecular mobility responsible for recrystallization is significantly reduced and the amorphous form is retained over long periods of time. $T_{g\beta}$ can therefore be thought of as the lowest temperature limit above which recrystallization might occur [21]. This finding agrees with other studies that have found evidence of crystal nucleation at temperatures well below the $T_{g\alpha}$ as for example, in indomethacin where crystallization has been observed at temperature as low as $T_{g\alpha}$ - 55 K [21], or for 3,3'– dimethoxy- 4,4'-bis(2,2-diphenylvinyl) biphenyl at $T_{g\alpha}$ -175 K [25] and for amorphous naproxen at $T_{g\alpha}$ - 89 K [19]. In addition, stability of proteins has been found to correlate with β-relaxation processes [24] and small organic molecules (detail review in [13]) have been shown to have a correlation with the β-relaxation time and crystallization kinetics.

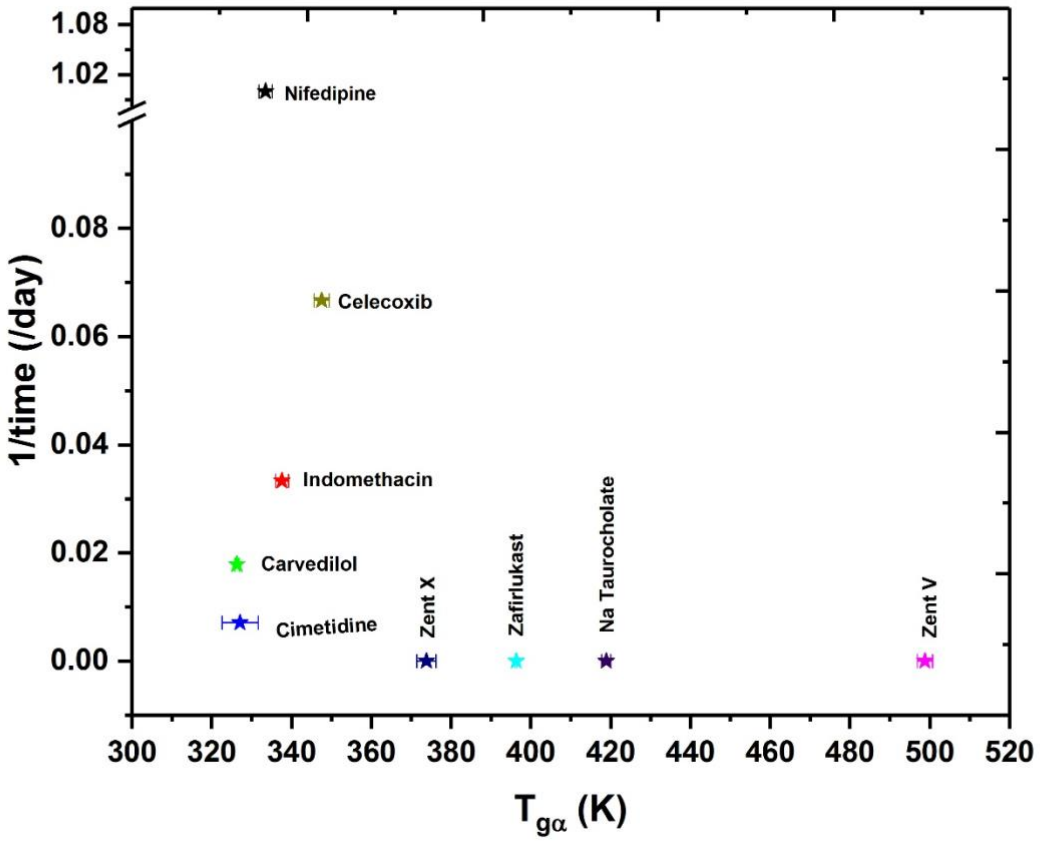


Figure 2: Lack of correlation between $T_{g\alpha}$ and the onset of recrystallization (1/time (/day)). At the chosen storage condition of 0% RH, 296 K, the $T_{g\alpha}$ does not provide adequate information on the physical stability.

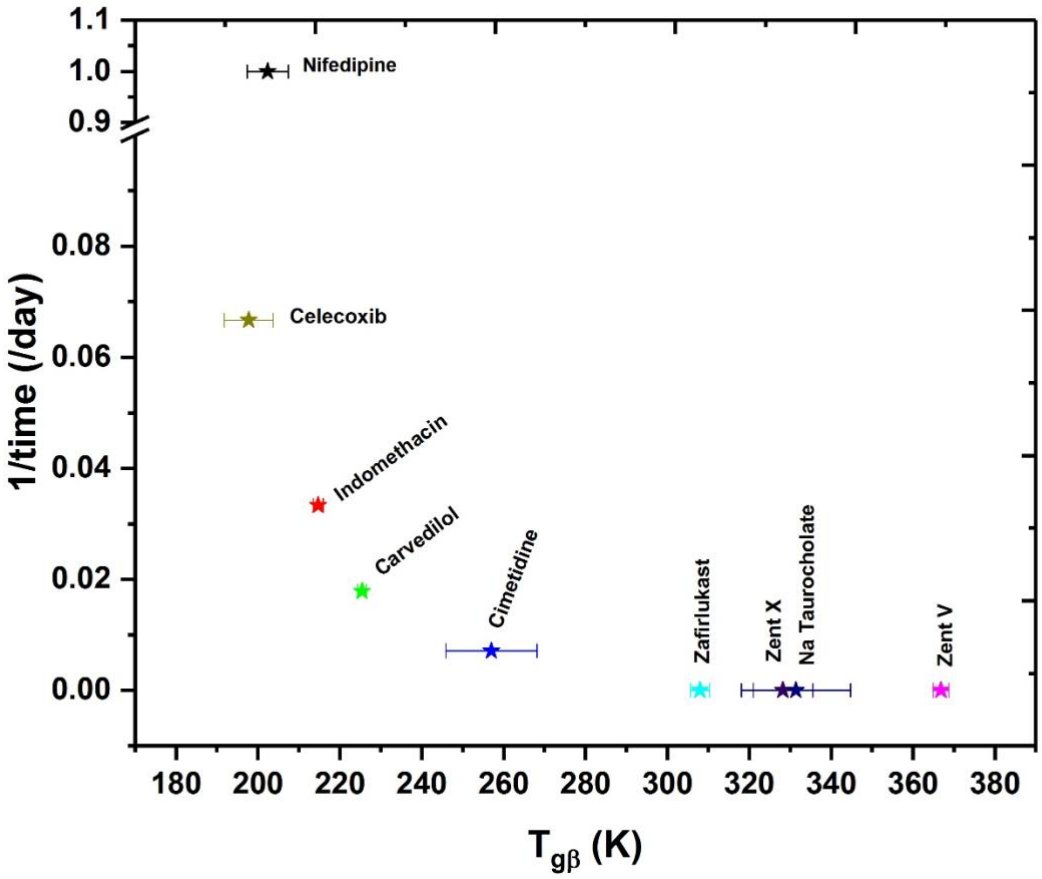


Figure 3: Correlation between $T_{g\beta}$ and onset of recrystallization (1/time (/day)). At the experimental storage condition, there is a correlation between $T_{g\beta}$ and physical stability.

As a rule of thumb, it has generally been assumed that molecular motion ceases when storing amorphous drugs at or below their Kauzmann temperature [46] which is estimated at 50 K below the $T_{g\alpha}$ [15, 47]. This assumption may not be valid as shown on the example of the most unstable drug in our sample set, nifedipine which has $T_{g\alpha}$ at 322.5 K. Storing nifedipine at 278 K guarantees physical stability for less than 4 days and at 253 K for under 136 days. In Figure 4, it is shown that decreasing the storage temperature increases nifedipine's resistance to recrystallization significantly. Therefore, physical stability increases with decreasing the storage temperature. From the results obtained, the

"T_g -50 K rule of thumb" [15, 47] may be rephrased as; "at a storage temperature $T_S < T_{g\beta}$ molecular motion responsible for recrystallization is reduced sufficiently, to render the amorphous form physically stable". Although for some amorphous drugs, $T_{g\beta}$ may be close to "$T_{g\alpha}$-50 K", it should be mentioned, that in our experiments we did not find a relation between the molecular processes happening at $T_{g\beta}$ and $T_{g\alpha}$. As an example, although nifedipine and indomethacin have similar $T_{g\alpha}$ (approx. 336 K), the difference between the individual $T_{g\beta}$ is well over 15 K.

For recrystallization of amorphous drugs, Sibik et al. [19] and Ruggiero et al. [41] have hypothesized that below $T_{g\beta}$ molecules do not have enough energy to overcome potential energy barriers and hence recrystallization is not possible for the disordered molecules. This explanation then implies that at temperatures below $T_{g\beta}$ the system becomes confined to individual potential energy minima, effectively 'locking' the molecules in and preventing large scale conformational rearrangement [41, 48]. This is in line with the suggestion by Middleton and Wales, where the lack of non-diffusive rearrangement [49] will result in no crystallization. Here we have provided experimental evidence (Figure 4 on NIF E) for this hypothesis. The amorphous form of the least physically stable of the nine drugs, nifedipine, is retained when stored at 193 K, i.e. below the $T_{g\beta}$ of this drug. Based on these experimental findings, it is justified that $T_{g\beta}$ is of importance compared to the relaxation time.

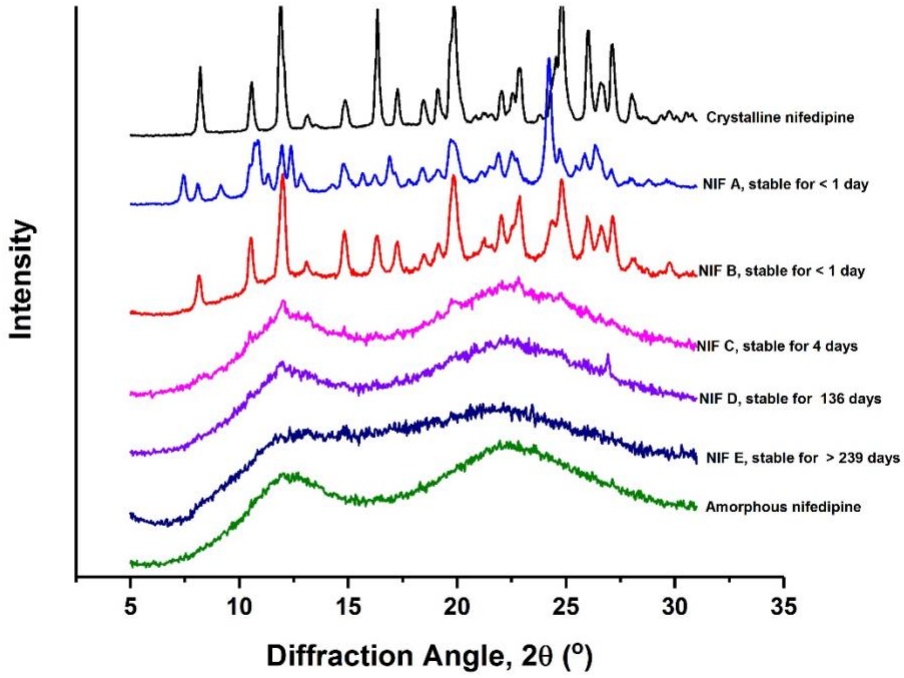


Figure 4: Diffractograms of amorphous nifedipine (NIF) stored at 0 % RH and at different temperatures; NIF A was stored at 313 K, NIF B was stored at 296 K, NIF C was stored at 278 K, NIF D 253 K and NIF E was stored at 193 K.

Based on the observed correlation between $T_{g\beta}$ and the physical stability, an empirical correlation is proposed for predicting the physical stability of neat amorphous drugs stored at 0% RH. This empirical correlation, as shown in Figure 5, was created by fitting an exponential curve of the form $y = Ae^{(-x/b)} + Ce^{(-x/d)} + y_0$ to the data in Figure 4, where *y* is the onset of recrystallization, *x* is $T_{g\beta}$ and *A, b, C, d* are constant values (fitting parameters are provided in supporting information). For celecoxib and nifedipine, that deviate somewhat from the proposed correlation, it was observed that the width of the peak associated with the β-relaxation in the DMA data was well over 50 K, whereas the other QC drugs were between 30-40 K (width of the β-relaxation of quench cooled drugs are shown in the supporting information). The broadness of the β-relaxation peak in the DMA data might imply that there is a wide temperature and energy range that the motions associated with the β-relaxation are related to, thus inherent errors and deviations might be more expected for these materials in comparison to the others. From this empirical correlation, the physical stability of neat amorphous drugs can be estimated. The curve flattens from 296 K and for drug molecules that have a $T_{g\beta}$ above this temperature, molecular mobility at or below RT responsible for crystallization might be low. Amorphous drugs that show $T_{g\beta}$ at or above RT might therefore, be physically stable and can be considered for pharmaceutical development. Also, many metallic glasses have a high $T_{g\beta}$ (e.g. $T_{g\beta}$ for $La_{56.16}Ce_{14.04}Ni_{19.8}Al_{10}$ metallic glass is 399 K [50]) and are practically stable at RT [34].

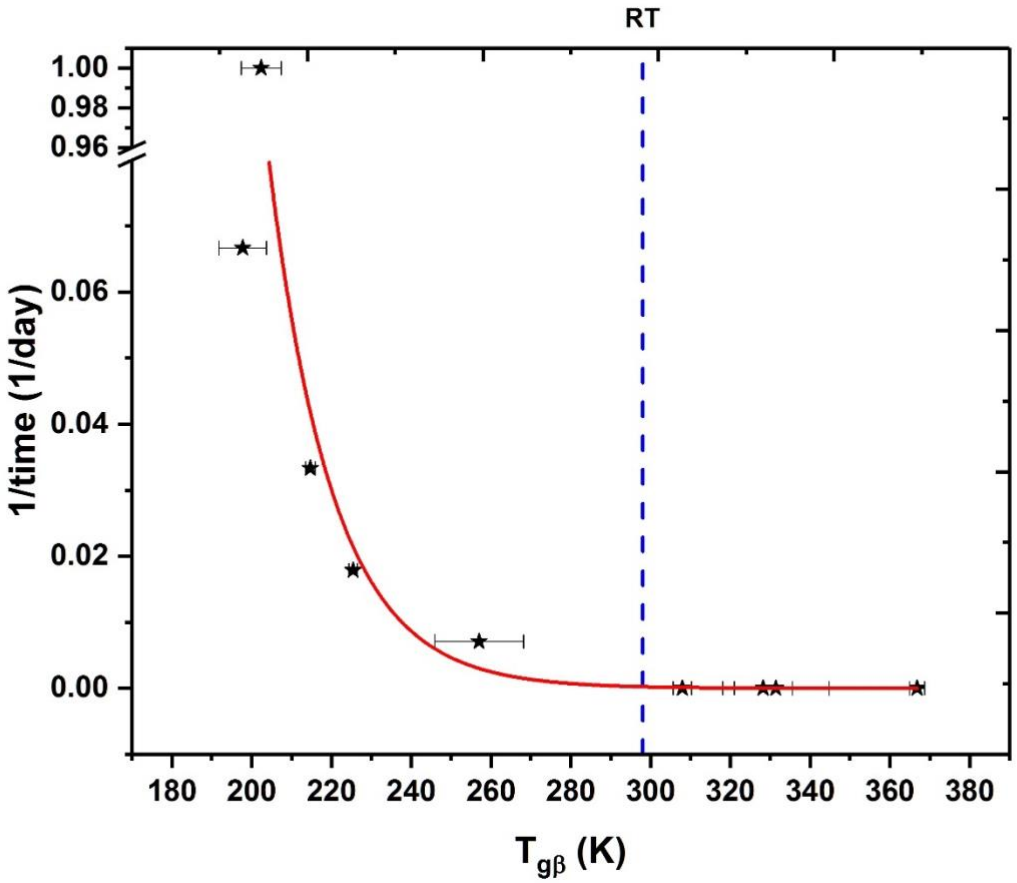


Figure 5: Based on the observed correlation, an empirical correlation for predicting the onset of recrystallization is proposed and drugs that have a $T_{g\beta}$ at or above ambient temperature (blue dashed line) are physically stable.

CONCLUSION

In summary, the relaxations in a set of amorphous drugs were characterized by DMA. The drugs exhibit mobility below their respective $T_{g\alpha}$. When studying physical stability of amorphous drugs, the β-relaxation is the decisive parameter to provide adequate information on the onset of recrystallization. The study of this set of amorphous drugs has revealed a clear correlation between β-relaxation and physical stability, and an empirical correlation for predicting physical stability has been proposed for drugs stored at dry conditions.

CORRESPONDING AUTHOR

Email: thomas.rades@sund.ku.dk

ACKNOWLEDGMENT

Zent X and Zent V (real names concealed) are already amorphous drug molecules in development by Zentiva k. s. Prague, Czech Republic and EOK, HG, KL and TR thank Zentiva for supplying the samples. MRT and JAZ would like to acknowledge the U.K. Engineering and Physical Sciences Research Council (EP/N022769/1).

SUPPORTING INFORMATION

Supporting information contains tan δ results for zafirlukast and Zent X and fitting parameters for the proposed equation. A typical analysis on Trios® software and the width of the β-relaxation of quench cooled drugs are shown in the supporting information.

results for zafirlukast and Zent X and fitting parameters.

REFERENCE

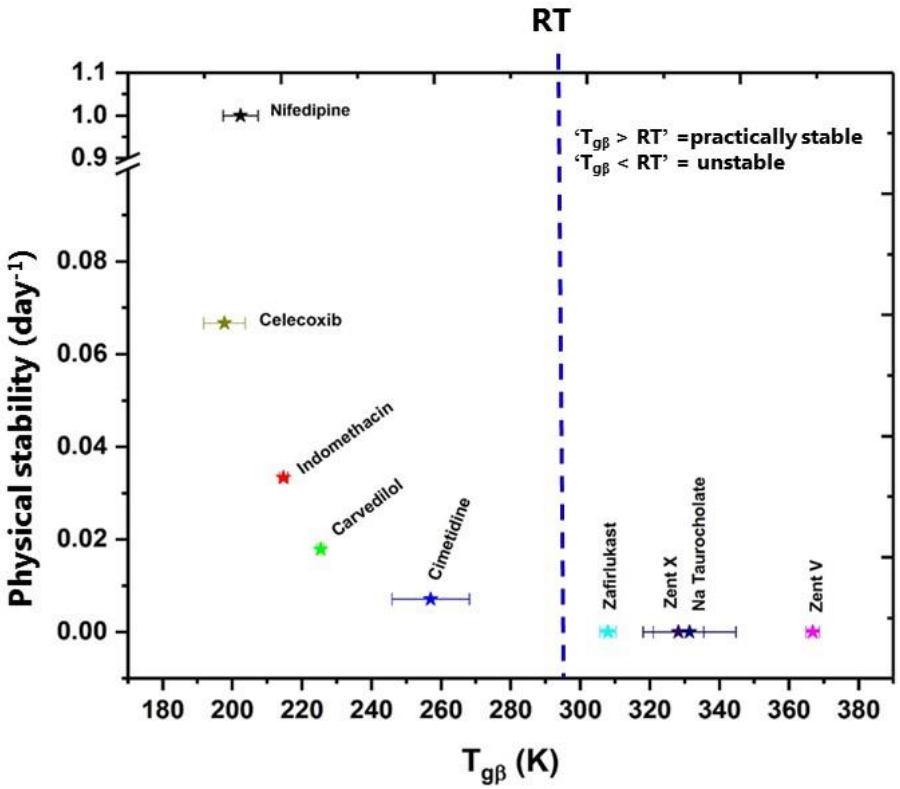
1. Lipp, R. The Innovator Pipeline: Bioavailability Challenges and Advanced Oral Drug Delivery Opportunities. *Am. Pharm. Rev.* **2013**, 16, 14-16.
2. Alhalaweh, A.; Alzghoul, A.; Mahlin, D.; Bergström, C. A. S. Physical Stability Of Drugs After Storage Above and Below the Glass Transition Temperature: Relationship To Glass-Forming Ability. *Int. J. Pharm.* **2015,** *495*, 312-317.
3. Nurzyńska, K.; Booth, J.; Roberts, C. J.; McCabe, J.; Dryden, I.; Fischer, P. M. Long-Term Amorphous Drug Stability Predictions Using Easily Calculated, Predicted, and Measured Parameters. *Mol. Pharmaceutics.* **2015,** *12*, 3389-3398.
4. Hancock, B. C.; Zografi, G. Characteristics and Significance of the Amorphous State in Pharmaceutical Systems. J. Pharm. Sci. **1997**, 86, 1-12.

5. Kirsten A. Graeser; Patterson, J. E.; Rades, T. Applying Thermodynamic and Kinetic Parameters to Predict the Physical Stability of Two Differently Prepared Amorphous Forms of Simvastatin. Curr. Drug Delivery **2009**, 6, 374-382.
6. Graeser, K. A.; Patterson, J. E.; Zeitler, J. A.; Gordon, K. C.; Rades, T. Correlating Thermodynamic and Kinetic parameters with Amorphous Stability. Eur. J. Pharm. Sci. **2009**, 37, 492-498.
7. Gupta, P.; Chawla, G.; Bansal, A. K. Physical Stability and Solubility Advantage from Amorphous Celecoxib: The Role of Thermodynamic Quantities and Molecular Mobility. Mol. Pharmaceutics **2004**, 1, 406-413.
8. Bhugra, C.; Pikal, M. J. Role of Thermodynamic, Molecular, and Kinetic Factors in Crystallization from the Amorphous State. J. Pharm. Sci. **2008**, 97, 1329-1349.
9. Zhou, D.; Zhang, G. G.; Law, D.; Grant, D. J.; Schmitt, E. A. Thermodynamics, Molecular Mobility and Crystallization Kinetics of Amorphous Griseofulvin. Mol. Pharmaceutics **2008**, 5, 927-36.
10. Talja, R. A.; Roos, Y. H. Phase and State Transition Effects on Dielectric, Mechanical, and Thermal Properties of Polyols. Thermochimica Acta **2001**, 380, 109-121.
11. Surana, R.; Pyne, A.; Suryanarayanan, R. Effect of Preparation Method on Physical Properties of Amorphous Trehalose. Pharm. Res. **2004**, 21, 1167-1176.
12. Bhattacharya, S.; Suryanarayanan, R. Local Mobility in Amorphous Pharmaceuticals-Characterization and Implications on Stability. J. Pharm. Sci. **2009**, 98, 2935-2953.
13. Grzybowska, K.; Capaccioli, S.; Paluch, M. Recent Developments in the Experimental Investigations of Relaxations in Pharmaceuticals by Dielectric Techniques at Ambient and Elevated Pressure. Adv. Drug Delivery Rev. **2016**, 100, 158-182.
14. Hoppu, P.; Hietala, S.; Schantz, S.; Juppo, A. M. Rheology and Molecular Mobility of Amorphous Blends of Citric Acid and Paracetamol. Eur. J. Pharm. Biopharm. **2009**, 71, 55-63.
15. Hancock, B.; Shamblin, S.; Zografi, G. Molecular Mobility of Amorphous Pharmaceutical Solids Below Their Glass Transition Temperatures. Pharm. Res. **1995**, 12, 799-806.
16. Cavaille, J. Y.; Perez, J.; Johari, G. P. Molecular Theory for the Rheology of Glasses and Polymers. Phys Rev B Condens Matter **1989**, 39, 2411-2422.
17. Qi, S. Thermal Analysis of Pharmaceuticals. In Analytical Techniques in the Pharmaceutical Sciences, Anette Müllertz, Y. P., Thomas Rades, Ed. Advances in Delivery Science and Technology: **2016**.
18. Paluch, M.; Roland, C. M.; Pawlus, S.; Zioło, J.; Ngai, K. L. Does the Arrhenius Temperature Dependence of the Johari-Goldstein Relaxation Persist above Tg? Phys. Rev. Lett. **2003**, 91, 115701.
19. Sibik, J.; Lobmann, K.; Rades, T.; Zeitler, J. A. Predicting Crystallization of Amorphous Drugs with Terahertz Spectroscopy. Mol. Pharmceutics. **2015**, 12, 3062-8.
20. Hikima, T.; Hanaya, M.; Oguni, M. Microscopic Observation of a Peculiar Crystallization in the Glass Transition Region and β-process as Potentially Controlling the Growth Rate in Triphenylethylene. J. Mol. Struct. **1999**, 479, 245-250.

21. Vyazovkin, S.; Dranca, I. Effect of Physical Aging on Nucleation of Amorphous Indomethacin. J. Phys. Chem. B **2007**, 111, 7283-7287.
22. Mehta, M.; Ragoonanan, V.; McKenna, G. B.; Suryanarayanan, R. Correlation between Molecular Mobility and Physical Stability in Pharmaceutical Glasses. Mol. Pharmaceutics **2016**, 13, 1267–1277.
23. Ichitsubo, T.; Matsubara, E.; Yamamoto, T.; Chen, H. S.; Nishiyama, N.; Saida, J.; Anazawa, K. Microstructure of Fragile Metallic Glasses Inferred from Ultrasound-Accelerated Crystallization in Pd-based Metallic Glasses. Phys. Rev. Lett. **2005**, 95 (24), 245501.
24. Cicerone, M. T.; Douglas, J. F. β-Relaxation Governs Protein Stability in Sugar-glass Matrices. Soft Matter **2012**, 8, 2983-2991.
25. Okamoto, N.; Oguni, M. Discovery of Crystal nucleation Proceeding much Below the Glass Transition Temperature in a Supercooled Liquid. *Solid State Commun.* **1996,** *99* (1), 53-56.
26. Clas, S. D.; Lalonde, K.; Khougaz, K.; Dalton, C. R.; Bilbeisi, R. Detection of a Minor Amorphous Phase in Crystalline Etoricoxib by Dynamic Mechanical Analysis: Comparison with Raman spectroscopy and Modulated Differential Scanning Calorimetry. J. Pharm. Sci. **2012**, 101, 558-65.
27. Jones, D. S.; Tian, Y.; Abu-Diak, O.; Andrews, G. P. Pharmaceutical applications of dynamic mechanical thermal analysis. Adv. Drug Delivery Rev. **2012**, 64, 440-448.
28. Abiad, M. G.; Campanella, O. H.; Carvajal, M. T. Assessment of Thermal Transitions by Dynamic Mechanical Analysis (DMA) Using a Novel Disposable Powder Holder. Pharmaceutics **2010**, 2, 78.
29. Royall, P. G.; Huang, C. Y.; Tang, S. W.; Duncan, J.; Van-de-Velde, G.; Brown, M. B. The development of DMA for the detection of amorphous content in pharmaceutical powdered materials. Int. J. Pharm. **2005**, 301, 181-91.
30. Mahlin, D.; Wood, J.; Hawkins, N.; Mahey, J.; Royall, P. G. A Novel Powder Sample Holder for the Determination of Glass Transition Temperatures by DMA. Int. J. Pharm. **2009,** 371, 120–125.
31. Ngai, K. L.; Paluch, M. Classification of Secondary Relaxation in Glass-Formers Based on Dynamic Properties. J. Chem. Phys. **2004**, 120, 857-873.
32. Ngai, K. L.; Capaccioli, S.; Shinyashiki, N.; Thayyil, M. S. Recent Progress in Understanding Relaxation in Complex Systems. J. Non-Cryst. Solids **2010**, 356, 535-541.
33. Sibik, J.; Zeitler, J. A. Direct Measurement of Molecular Mobility and Crystallisation of Amorphous Pharmaceuticals Using Terahertz Spectroscopy. Adv. Drug Delivery Rev. **2016**, 100, 147–157.
34. Yu, H.-B.; Wang, W.-H.; Samwer, K. The β-relaxation in Metallic Glasses: an Overview. Materials Today **2013**, 16, 183-191.
35. Johari, G. P. Intrinsic mobility of molecular glasses. J. Chem. Phys 1973, 58, 1766-1770.
36. Heiman, D.; Hamilton, D. S.; Hellwarth, R. W. Brillouin Scattering Measurements on Optical Glasses. Phys. Rev. B **1979**, 19, 6583-6592.
37. Carpenter, J. M.; Price, D. L. Correlated Motions in Glasses Studied by Coherent Inelastic Neutron Scattering. Phys. Rev. Lett. **1985**, 54, 441-443.

38. Liem, H.; Cabanillas-Gonzalez, J.; Etchegoin, P.; Bradley, D. D. C. Glass Transition Temperatures of Polymer Thin Films Monitored by Raman scattering. J. Physics: Condensed Matter **2004**, 16, 721.
39. Schnauss, W.; Fujara, F.; Sillescu, H. The Molecular Dynamics Around the Glass Transition and in the Glassy State of Molecular Organic Systems: A $^{2}H-$Nuclear Magnetic Resonance Study. J. Chem. Phys. **1992**, 97, 1378-1389.
40. Vyazovkin, S.; Dranca, I. Probing Beta Relaxation in Pharmaceutically Relevant Glasses by Using DSC. Pharm. Res. **2006**, 23, 422-428.
41. Ruggiero, M. T.; Krynski, M.; Kissi, E. O.; Sibik, J.; Markl, D.; Tan, N. Y.; Arslanov, D.; van der Zande, W.; Redlich, B.; Korter, T. M.; Grohganz, H.; The Significance of the Amorphous Potential Energy Landscape for Dictating Glassy Dynamics and Driving Solid-State Crystallisation. Phys. Chem. Chem. Phys. 2017, 19, 30039-30047
42. Fujimori, H.; Oguni, M. Construction of an adiabatic calorimeter at low temperatures and glass transition of crystalline 2-bromothiophene. *J. Phys. Chem. Solids* **1993,** *54*, 271-280.
43. Ngai, K. L.; Capaccioli, S.; Prevosto, D.; Wang, L.-M. Coupling of Caged Molecule Dynamics to JG β-Relaxation II: Polymers. *The Journal of Physical Chemistry B* **2015,** *119*, 12502-12518.
44. Ngai, K. L.; Capaccioli, S.; Prevosto, D.; Wang, L.-M. Coupling of Caged Molecule Dynamics to JG β-Relaxation III:van der Waals Glasses. *The Journal of Physical Chemistry B* **2015,** *119*, 12519-12525.
45. Capaccioli, S.; Ngai, K. L.; Thayyil, M. S.; Prevosto, D. Coupling of Caged Molecule Dynamics to JG beta-Relaxation: I. *J. Phys. Chem. B* **2015,** *119*, 8800-8.
46. Kauzmann, W. The Nature of the Glassy State and the Behavior of Liquids at Low Temperatures. *Chem. Rev.* **1948,** *43*, 219-256.
47. Yu, L. Amorphous pharmaceutical solids: preparation, characterization and stabilization. *Advanced Drug Delivery Reviews* **2001,** *48*, 27-42.
48. Cicerone, M. T.; Tyagi, M. Metabasin transitions are Johari-Goldstein relaxation events. *The Journal of Chemical Physics* **2017,** *146*, 054502.
49. Middleton, T. F.; Wales, D. J. Energy Landscapes of some Model Glass Formers. *Phys. Rev. B* **2001,** *64*, 024205
50. Wang, Q.; Zhang, S. T.; Yang, Y.; Dong, Y. D.; Liu, C. T.; Lu, J. Unusual Fast Secondary Relaxation in Metallic Glass. *Nat Commun* **2015,** *6*.

Graphical Abstract



$T_{g\beta}$ correlates with the physical stability of amorphous drugs